How should prostate specific antigen be interpreted?

Ali Atan, Özer Güzel

ABSTRACT

Since from its clinical introduction to the present time, measurement of serum prostate specific antigen (PSA) level is one of the most widely used tests in urology practice. Initially, the upper limit for PSA was 4 ng/mL, but today, a reduction for the upper limit is recommended to 2.5-3 ng/mL for patients between 60 and 65 years of age and younger. On the use of PSA as a screening test for prostate cancer, there are differences of opinion. However, it is a recommended test in the evaluation and monitoring of the risky group for prostate cancer. In conclusion PSA test should be performed at appropriate intervals for appropriate people with an appropriate age, after informing the patient about the test in detail.

Key words: Male, PSA, screening

Prostate- specific antigen (PSA) is a glycoprotein secreted from prostatic acini, and it is firstly defined in the year 1979.^[1] US Food and Drug Association (FDA) approved PSA as an auxiliary diagnostic test in the management of the patients diagnosed as prostate cancer (PCa).^[2] It was introduced into clinical practice in 1987 as a diagnostic marker.^[3] Catalona 1991 recommended use of PSA as a screening test for PCa.^[4] Later on, in the year 1994 FDA approved PSA as a diagnostic test for early detection of PCa.

From its introduction into clinical practice up to present, measurement of serum PSA levels is still one of the most frequently used tests among urological tests. However, as has been reported, tests have been performed without adequately informing patients about advantages, and disadvantages of PSA measurement.^[2-4] Nowadays, guidelines of American Urological Association, American Cancer Society, and United States Preventive Services Task Force require mutual decision between the physician, and the patients about performing PSA test.^[5]

Upper limit of normal (ULN) for prostate-specific antigen was recommended as 4 ng/mL when it was firstly introduced into clinical practice. This cut-off value was based on serum PSA measurements of 860 healthy men. All of these male population under 40 years

of age had serum PSA levels below 4 ng/mL, while 97% of the men over 40 years of age had PSA values below 4 ng/mL. Based on these data, a cut-off value of 4 ng/mL has been deemed to be appropriate.^[6] Serum PSA levels can increase because of impairment of normal prostatic anatomy secondary to prostatic diseases (benign prostatic hyperplasia, prostate cancer, and prostatitis), and prostatic trauma because of entry of excessive amounts of PSA into general circulation.^[7,8] Morphological structure of the benign prostatic tissue does not effect serum PSA levels. Benign prostatic hyperplasia (BPH) has stromal, glandular or mixed types. In every patient type of BPH differs. In other words, in some people stromal BPH is the predominant type, and in some, glandular hyperplasia is in the foreground. In some group of people, mixed hyperplasia with equal proportions of both components can be observed. However any correlation between this type of hyperplasia, and serum PSA level has not been detected.^[9]

Serum PSA level is very important for urologists. Indeed prostate cancer (PCa) is the most frequently type of cancer encountered in men in Europe, and the USA.^[10] In the pre-PSA era for the diagnosis, staging, and follow-up of PCa, prostatic acid phosphatase (PAP), and digital rectal examination (DRE) were being used. These methods were generally used for

Department of Urology, Ankara Numune Training and Research Hospital, Ankara, Turkey,

Submitted:
18.02.2013

Accepted:
30.04.2013

Correspondence:
Ali Atan
Department of Urology, Ankara Numune Training and Research Hospital, 06100 Ankara, Turkey
Phone: +90 312 430 06 97
E-mail: aliatanpitt@hotmail.com

©Copyright 2013 by Turkish Association of Urology

Available online at
www.turkishjournalofurology.com

the diagnosis of advanced stage PCa. While they could only detect 20-30% of the organ-confined disease, and most of the cases were overlooked. Introduction of PSA test into clinical practice has enabled early diagnosis of PCa, and provided important information about staging, and postoperative follow-up period.

a. Early diagnosis: After introduction of serum PSA measurements into clinical use, the incidence rate of early diagnosis has increased, and a shift between stages was achieved. Nowadays, 70-80% of the diagnosed cancers are organ-confined.^[11,12]

b. Staging: Serum PSA level was also helpful in the staging of PCa. Serum PSA values between 0-4 ng/mL can detect 80% of the organ-confined disease, while PSA values between 4-10 ng/mL, and above 10 ng/mL were found in 70, and 50% of the cases with organ-confined disease. Serum PSA levels also provide us helpful information about lymph node involvement. Lymph node involvement has been also reported in men with serum PSA levels of <10 ng/mL (5%), 10-20 ng/mL (18%), and >20 ng/mL (20%) in respective percentages. Therefore, if serum PSA level is below 25 ng/mL, there is no need to perform CT or MRI, and bone scanning is not required for men with serum PSA levels below 20 ng/mL. Besides, it has been demonstrated that in men with Gleason score ≤ 6 , clinical stage T1/T2, and serum PSA levels below 10 ng/mL, lymph node dissection is not required.^[8]

c. Follow-up: Measurement of serum PSA levels is very important during post-treatment monitorization of PCa. A PSA value below 0.2 ng/mL following radical surgery is considered as a cure, while after curative radiotherapy a PSA value below 2 ng/mL is anticipated. Besides based on preoperative serum PSA levels, a biochemical recurrence can be seen within 10 years after surgery. Accordingly, recurrence rates of 10, 20, and 50% are anticipated in men with preoperative serum PSA levels of <2.6 ng/mL, 2.6-10 ng/mL, and above 10 ng/mL, respectively. Serum PSA levels are important in patients who had undergone androgen suppression therapy because of metastatic disease. If serum PSA level does not drop below 4 ng/mL 7 months after androgen suppression therapy, median life-expectancy of these patients is only one year. If serum PSA levels of these patients drop below 0.2 ng/mL, then median life-expectancy longer than 6 years can be predicted. If after radical prostatectomy or radiotherapy, serum PSA levels of the patients without radiological metastases rise above 0.2 ng/mL within the first 8 months of androgen suppression, prostate cancer mortality increases 20-fold. Still PSA doubling time shorter than 3 months is a very bad prognostic finding.^[8] Rise in serum PSA levels after prostatectomy aids in differentiation between local, and systemic recurrences. If PSA doubling time increases after the first 2 postoperative years, and PSA doubling time is longer than 11 months, then local recurrence should be conceived with

a 80% probability. However if PSA levels rise within the first postoperative year, and PSA doubling time is 4-6 months, then systemic disease should be thought of with a 80% probability.^[13]

Even though serum PSA levels provide quite helpful information about PCa, PSA not an ideal marker. An ideal marker should be disease-specific, lead to early diagnosis, and rule out clinically insignificant disease. Besides, it should be easily applicable, cost-effective, standard, and provide valuable information about staging, and posttreatment monitorization. We know that despite benefits of serum PSA measurements in diagnosis, staging, and follow-up, they have several limitations. Since PSA is not specific to prostatic disease, it can not absolutely discriminate between benign, and malignant prostatic diseases. Serum PSA level between 0-4 ng/mL has a 20% diagnostic sensitivity, and 60-70% specificity for PCa. Besides it fails to differentiate between clinically significant, and insignificant prostatic diseases.^[8] Some modifications have been implemented to increase sensitivity, and specificity of serum PSA level. These include PSA density (PSAD, $>$ or < 0.15), PSA velocity, f/t PSA ratio (25%; sensitivity 95%), and decreased threshold value (2.5, and 3 ng/mL). Initially, for the total PSA value between 4-10 ng/mL, a cut-off value of ≥ 0.75 ng/mL has been accepted for PSA velocity. Nowadays, a cut-off value of ≥ 0.4 ng/mL for PSA velocity has been recommended in the presence of total PSA values of < 4 ng/mL in patients younger than 60 years of age. At least 3 measurements should be made during 18 months for the determination of PSA velocity.^[8,14,15] However, despite all modifications, a reliable serum PSA value is not available. Indeed PCa can be observed in every PSA level. As explicitly demonstrated in a study by Thompson, PCa can be detected in PSA levels of 0-0.5 ng/mL (6.6%), 0.6-1 ng/mL (10.1%), 1-2 ng/mL (17.2%), 1-3 ng/mL (23.9%), 3.1-4 ng/mL (26.9%), at respective incidence rates.^[16] Therefore, it will be helpful to inform patients about PSA before PSA test.

Despite all of these problematic issues about serum PSA levels, PSA test is the most frequently used test, and we concern about PCa when we detect increased serum PSA levels. Indeed, it is not possible to identify the prostatic disease based on DRE findings, and increased serum PSA levels. In the presence of a serum PSA level above its cut-off value, histopathological examination of the prostate biopsy specimen should be absolutely performed in order to establish tissue diagnosis. Since we don't know completely biological behaviour, and natural course of the cancers diagnosed with the aid of prostate biopsy which is an invasive procedure with its certain septic, and traumatic complications, we are compelled to offer patients various treatment alternatives with several complications. Therefore, necessity of widespread use of PSA test is debatable. Four large-scale population based studies investigated this issue including The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,

European Randomized Study of Screening Prostate Cancer (ERSPC), Norrköping Prostate Cancer Screening Trial, and Göteborg Prostate Cancer Screening Trial. The PLCO trial demonstrated that within a 7-10 year-period prostate cancer screening had not any significant impact on prostate cancer related mortality.^[17] In the screening group of the ERSPC trial, prostate cancer-related mortality could be decreased at a rate of 20 percent. It was determined that to prevent death of a single patient 1410 men should be screened, and 48 PCa patients should be treated.^[18] However in the Norrköping trial the researchers indicated lack of any significant impact of screening on mortality during 20 years of monitorization.^[19] In the Göteborg trial, at the end of 14 years of the follow-up period the investigators concluded that screening has beneficial effects, and for the prevention of death of one patient, 293 men should be screened, and 12 patients should be treated.^[20] Data of the first 3 trials disfavoured PSA screening, while the Göteborg trial indicated that PSA screening was effective in decreasing PCa-specific mortality rates. However none of these population-based studies is ideal, and they have various limitations. Therefore, the results acquired have not gained general acceptance.^[21] Whereas, data of other studies suggested beneficial effects of PSA screening tests. Data of US Surveillance, Epidemiology and End Results (SEER) study demonstrated a 40% decrease in age-adjusted PCa-specific mortality rates between the years 1992, and 2007. This increase in mortality was attributed to increased use of PSA tests.^[21] The researchers have found that in the United States of America, Canada, France, Germany, and Spain, where PSA tests were routinely used, PCa-related mortality decreased, while in countries where PSA tests were not routinely performed including Belgium, Denmark, Greece, Ireland, and Bulgaria, PCa-specific mortality rates increased steadily.^[22-24] Besides, in the Austrian state of Tyrol where PSA tests were routinely used PCa-related mortality rates decreased 54%, while in other regions of Austria where PSA tests were not routinely performed, mortality rates decreased only at a rate of 29 percent.^[25] Based on these data, PSA screening apparently decreases PCa-related mortality rates.

There is a difference of opinion among various national organizations concerning use of PSA test for prostate cancer screening. United States Preventive Services Task Force, American College of Preventive Medicine, Royal Australian College of General Practitioners, Cancer Council Australia do not recommend use of PSA screening tests. Urological Association of Australia, and New Zealand, Prostate Cancer Foundation of Australia, American Urological Association, and American Cancer Society recommend use of PSA as a PCa screening test. As a remarkable finding non-urological associations have not recommended PSA screening tests, while urological associations have favoured PSA screening.^[8,21] In 2012 European Association of Urology guideline, starting age for PSA test is

lowered, while widespread PSA screening is not found to be appropriate.^[26]

Generally speaking, the reason for not recommending PSA screening is that in men with a biopsy proven diagnosis of PCa, some of these cancers are clinically insignificant cancers. Radical prostatectomy specimens of a total of 247 patients with a diagnosis of PCa included in ERSPC study were evaluated as for the evidence of prostate cancer, and clinically insignificant indolent cancers were detected in 49% of the patients.^[27] As reported in a more recent study, between 1986, and 2005 more than one million men in the United States of America were overdiagnosed, and thus overtreated.^[28] However, the subject of clinically insignificant cancers is still debatable. PSA level, PSAD, clinical stage, Gleason score, number of core biopsies with tumor, percentage, extension, and volume of the tumor in core biopsies are parameters which have been analyzed in the discrimination between clinical significant, and insignificant cancers.^[29] Only clinical parameter which does not change in all studies regarding clinically insignificant PCa is Gleason score below 6. In addition, a tumor mass smaller than 3 mm in one core biopsy can be included among these parameters. On histopathological analysis, detection of tumor volume less than 0.5 cm³ is also another invariable characteristic of clinically insignificant cancer.^[29-31] However, currently, we haven't any accurate, and reliable measurement method for tumor volume. Therefore it is not always possible to accurately identify clinically insignificant cancer based on evaluation of clinical parameters.

Prostate-specific antigen is not disease, but organ-specific, and PCa can be detected at every PSA level. Besides increased number of overdiagnoses owing to PSA tests performed on every men have led to overtreatment of patients. Because of all these abovementioned reasons, priorities for PSA testing should be defined precisely. American Cancer Society, and American Urological Association do not recommend PSA tests for asymptomatic men with a life-expectancy less than 10 years because of his advanced age, and general health state.^[8,32] Their guidelines argue against PSA testing for men older than 75 years of age.^[21,26,33]

Another debatable issue is related to the time to start PSA control. American Cancer Society indicates that after informing the patient in detail, PSA testing should be initiated at age of 50 in an average risk patient, while in high (black race, PCa in the first-degree relative), and very high-risk groups (PCa in more than two first-degree relatives) PSA test should be performed beginning from 45, and 40 years of age, respectively.^[32] However, National Comprehensive Cancer Network recommends DRE, and PSA testing in men over 40 years of age after informing patients in detail.^[34] American Urological

Association, and European Association of Urology also recommend PSA controls beginning from 40 years of age.^[35] Indeed, the first PSA measurement provides important information about PCa which might develop in the future. The first PSA measurement over median value is a risk factor for PCa. Upper limit of normal of age-adjusted median PSA values for various age groups have been determined as follows: 0.7 ng/mL (40-50 yrs), 0.8 ng/mL (50-60 yrs), 1.2 ng/mL (60-70 yrs), and 1.5 ng/mL (>70 yrs). These PSA levels have been indicated as significant determinative factors for PCa which are more valuable than family history, race, and DRE findings.^[36]

Time intervals between PSA measurements are not firmly established. American Cancer Society (ACS) recommend monitoring of PSA levels annually or every other year if the first measured PSA levels are lower than 2.5 ng/mL or 2.5-4 ng/mL, respectively. However ACS also indicates that these time intervals may change based on individualized risk [black race, family history, abnormal DRE findings, and advanced age] assessment. ACS also asserts that if serum PSA level is above 4 ng/mL, then absolutely further evaluation, and in case of need, biopsy should be considered.^[32] National Comprehensive Cancer Network recommends yearly measurements of serum PSA levels in men with PSA values above 1 ng/mL or in black men. If the first measured PSA level is below 1 ng/mL, then it is appropriate to monitor PSA levels at age 45, if it is still at that level third measurement can be done at age 50, and then at yearly intervals.^[34] Stricker et al.^[21] recommended a PSA control algorithm in the year 2012 based on risk level of the patient. Accordingly, after informing the patient in detail, based on the general health state of the patient, and their firstly measured serum PSA levels, PSA monitoring is advised within age intervals of 40-59, 60-70 years, and after age of 71.

a. In men aged over 40 years with a life-expectancy of more than 10 years, PSA test can be performed after informing patient in detail. In men in the 40-59 age group with the first measured PSA value above 3 ng/mL urological examination is a must. If the first measured PSA levels are 1.5-3 ng/mL, 0.6-1.5 ng/mL or below 0.6 ng/mL, then it will be appropriate to monitor PSA levels annually, every 2 years or 7 years later, respectively.

b. In men aged between 60-70 years without a life-expectancy longer than 10 years because of comorbidities, PSA monitoring is not required. However if the first PSA measurement is above 3 ng/mL in men with a life-expectancy of more than 10 years, then urological examination is mandatory. If the first measured PSA value is >2 ng/mL or 1-2 ng/mL, then serum PSA levels should be controlled annually or every other year, respectively. If the first measured PSA level is below 1 ng/mL, then there is no need for PSA control.

c. In men aged 71 years without a life-expectancy of more than 10 years PSA controls are not required. In men aged 71-75 with a life-expectancy of more than 10 years, if PSA value is higher than age-adjusted PSA value (6.5 ng/mL) or abnormal DRE findings are detected then an urological examination is required. If age-adjusted PSA values are between 3-6.5 ng/mL, then yearly controls should be performed.

d. In men over 75 years of age with PSA levels below 3 ng/mL, PSA monitorization is not required.

Since prostate-specific antigen is a specific marker for prostate, the correlation between BPH, and serum PSA levels is another important issue worth considering. Therefore, serum PSA level can provide critically important information about prostate volume, lower urinary tract symptoms (LUTS), bladder outlet obstruction (BOO), and treatment preference for patient's BPH. We know that serum PSA levels elevate as prostate volume increases. Critical value for prostatic enlargement has been also determined (30 cc). Indeed, in cases with bigger prostates (>30 cc), moderate-severe lower urinary tract complaints increase 3.5 fold, maximum urine flow (Qmax) decreases 2.5-fold, and development of acute urinary retention (AUR) is observed 3-4 times more frequently relative to those with smaller prostates.^[37] Higher serum PSA levels (>1.5 ng/mL) have been detected in patients with prostate volumes over 30 cc.^[38,39] Serum PSA levels over 1.5 ng/mL, and prostate volume of >30 mL lead to progression of BPH. Progression of BPH means increase in the severity of LUTS, decrease in Qmax, and worsened AUR and/or enhanced need for surgical intervention.^[40] A correlation exists between serum PSA levels, and bladder outlet obstruction (BOO). It has been indicated that possibility of BOO increases at serum PSA levels above 4 ng/mL, while a clinically significant BOO is not observed at serum PSA levels below 2 ng/mL.^[41] It has been recommended that in the evaluation of BOO secondary to BPH, serum PSA levels should be taken into consideration.^[42] In the selection process of medical treatment for BPH, serum PSA levels convey importance. In patients with serum PSA levels above 1.5 ng/mL, 5- α -reductase inhibitor therapy has been found to be more effective.^[43-45]

Whatever the reason might be, the issue of collecting blood samples for serum PSA measurements at any hour of the day whether in the pre-, or postprandial period also carries importance. In our study the first blood sample was drawn at 8:00 AM from men who fasted overnight from 12:00 PM up to 8:00 AM in the next morning. Second, and third blood samples were collected 1, and 2 hours after the breakfast. Patients received their lunch at 12:00 AM. Two hours after lunch the last blood sample was drawn. Any intake of liquid or solid food was not allowed between meals. A significant difference in serum PSA levels measured at different time points during a 6-hour period was not

detected.^[46] According to our data, blood samples can be drawn for the measurement of serum PSA levels at any hour of the day independent of the fasting state of the patient.

In conclusion despite some limitations, till development of another marker, serum PSA level is a very important marker in the evaluation of prostatic diseases. To gather maximum benefit from serum PSA testing, the patient should be informed in detail about advantages, and disadvantages of PSA test, and after obtainement of undersigned consent forms from patients concerning PSA testing, PSA tests should be performed on suitable patients (patients aged >40 years with a risk factor, and a life expectancy of more than 10 years) at appropriate intervals determined in consideration of the first PSA value.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.A.; Design - A.A., Ö.G.; Supervision - A.A., Ö.G.; Funding - A.A., Ö.G.; Materials - A.A., Ö.G.; Data Collection and/or Processing - A.A., Ö.G.; Analysis and/or Interpretation - A.A., Ö.G.; Literature Review - A.A., Ö.G.; Writer - A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. *Invest Urol* 1979;17:159-63.
- Venderbos LD, Roobol MJ. PSA-based prostate cancer screening: the role of active surveillance and informed and shared decision making. *Asian J Androl* 2011;13:219-24.
- Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909-16.
- Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991;324:1156-61.
- Woolf SH, Krist A. Shared decision making for prostate cancer screening: do patients or clinicians have a choice? *Arch Intern Med* 2009;169:1557-9.
- Myrtle J, Ivor L. Measurement of PSA in Serum by two immunometric Methods (Hybritech Tandem-R/Tandem-E PSA). In: Catalona WJ (ed), *Clinical Aspects of Prostate Cancer*. New York, Elsevier. 1989.pp.161-71.
- Gjertson CK, Albertsen PC. Use and assessment of PSA in prostate cancer. *Med Clin North Am* 2011;95:191-200.
- Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. *J Urol* 2013;189:2-11.
- Atan A, Horn T, Hansen F, Jakobsen H, Hald T. Prostatic specific antigen and benign prostatic hyperplasia. *Scand J Urol Nephrol* 1996;30:299-302.
- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300.
- Mettlin C, Murphy GP, Lee F, Littrup PJ, Chesley A, Babaian R, et al. Characteristics of prostate cancers detected in a multimodality early detection program. The Investigators of the American Cancer Society-National Prostate Cancer Detection Project. *Cancer* 1993;72:1701-8.
- Catalona WJ. Treatment strategies for prostate cancer. *JAMA* 1993;270:1691.
- Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2011;59:572-83.
- van Renterghem K, Van Koeveringe G, Achten R, van Kerrebroeck P. A new algorithm in patients with elevated and/or rising prostate-specific antigen level, minor lower urinary tract symptoms, and negative multisite prostate biopsies. *Int Urol Nephrol* 2010;42:29-38.
- Gjertson CK, Albertsen PC. Use and assessment of PSA in prostate cancer. *Med Clin North Am* 2011;95:191-200.
- Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004;350:2239-46.
- Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310-9.
- Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. - *N Engl J Med* 2009;360:1320-8.
- Sandblom G, Varenhorst E, Rosell J, Löfman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. *BMJ* 2011;342:1539.
- Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11:725-32.
- Stricker PD, Frydenberg M, Kneebone A, Chopra S. Informed prostate cancer risk-adjusted testing: a new paradigm. *BJU Int* 2012;110:30-4.
- Bouchardy C, Fioretta G, Rapiti E, Verkooijen HM, Rapin CH, Schmidlin F, et al. Recent trends in prostate cancer mortality show a continuous decrease in several countries. *Int J Cancer* 2008;123:421-9.
- Kvåle R, Auvinen A, Adami HO, Klint A, Hernes E, Møller B, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst* 2007;99:1881-7.
- van Leeuwen PJ, Connolly D, Gavin A, Roobol MJ, Black A, Bangma CH, et al. Prostate cancer mortality in screen and clinically detected prostate cancer: estimating the screening benefit. *Eur J Cancer* 2010;46:377-83.

25. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101:374-83.
26. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. European Association of Urology EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011;59:61-71.
27. Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, de Koning HJ, Schröder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. *J Urol* 2007;177:107-12.
28. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. *J Natl Cancer Inst* 2009;101:1325-9.
29. Mouraviev V, Madden JF. Focal therapy for prostate cancer: pathologic basis. *Curr Opin Urol* 2009;19:161-7.
30. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA* 2010;304:2373-80.
31. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999;17:168-72.
32. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society Prostate Cancer Advisory Committee. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010;60:70-98.
33. Calonge N, Petitti DB, DeWitt TG, Dietrich AJ, Gregory KD, Harris R, et al. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:185-91.
34. Kawachi MH, Bahnson RR, Barry M, Busby JE, Carroll PR, Carter HB, et al. NCCN clinical practice guidelines in oncology: prostate cancer early detection. *J Natl Compr Canc Netw* 2010;8:240-62.
35. Zhu X, Albertsen PC, Andriole GL, Roobol MJ, Schröder FH, Vickers AJ. Risk-based prostate cancer screening. *Eur Urol* 2012;61:652-61.
36. Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology* 2006;67:316-20.
37. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med* 1998;338:557-63.
38. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999;53:581-9.
39. Mochtar CA, Kiemeny LA, van Riemsdijk MM, Barnett GS, Laguna MP, Debruyne FM, et al. Prostate-specific antigen as an estimator of prostate volume in the management of patients with symptomatic benign prostatic hyperplasia. *Eur Urol* 2003;44:695-700.
40. Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, et al. MTOPS RESEARCH Group. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* 2006;175:1422-7.
41. Laniado ME, Ockrim JL, Marronaro A, Tubaro A, Carter SS. Serum prostate-specific antigen to predict the presence of bladder outlet obstruction in men with urinary symptoms. *BJU Int* 2004;94:1283-6.
42. Bantis A, Zissimopoulos A, Kalaytzis C, Giannakopoulos S, Sountoulides P, Ageloniou E, et al. Correlation of serum prostate specific antigen, the volume and the intravesical prostatic protrusion for diagnosing bladder outlet obstruction in patients with benign prostate hyperplasia. *Hell J Nucl Med* 2007;10:138-43.
43. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G; ARIA3001 ARIA3002 and ARIA3003 Study Investigators. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002;60:434-41.
44. Bartsch G, Fitzpatrick JM, Schalken JA, Isaacs J, Nordling J, Roehrborn CG. Consensus statement: the role of prostate-specific antigen in managing the patient with benign prostatic hyperplasia. *BJU Int* 2004;93:27-9.
45. Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004;46:547-54.
46. Tuncel A, Aksut H, Agras K, Tekdogan U, Ener K, Atan A. Is serum prostate-specific antigen level affected by fasting and nonfasting? *Urology* 2005;66:105-7.